

NOTES

SPHINGOLIPIDOSIS

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Lysosomal storage diseases
- Metabolic disorders characterized by dysfunctional metabolism of sphingolipids
- Sphingolipids accumulate within various tissues' cell lysosomes → affected organ damage
- Causes genetic defects → lysosomal enzyme deficiency
- Inheritance mode autosomal recessive, except in Fabry disease (X-linked recessive)

SIGNS & SYMPTOMS

- Vary depending on organs affected, sphingolipid storage extent

DIAGNOSIS

- Clinical presentation, family history
- Enzymatic assays
- Mutation analysis

TREATMENT

- Enzyme replacement therapy
- Gene therapy

FABRY DISEASE

osms.it/fabry-disease

PATHOLOGY & CAUSES

- Lysosomal enzyme alpha **galactosidase A** (a-GAL A) **deficiency**
- → Accumulation of a sphingolipid, called glycosphingolipid, called ceramide trihexoside, within lysosomes
- Gb3 most commonly deposits in vessels, ganglia, kidneys, heart
- **X-linked recessive** inheritance pattern

COMPLICATIONS

- Affected organ dysfunction, vascular occlusions, infarctions

SIGNS & SYMPTOMS

- Early presentation
 - Acroparesthesias (severe peripheral neuropathic pain in extremities)
 - **Angiokeratomas** (painless red to blue papules with hyperkeratosis), Telangiectasias (dilated vessels) presenting on the skin
 - Gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting)
 - Corneal opacities

VISIT...

LANZAROTE
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Figure 52.1 Numerous angiokeratomas on the skin of an individual with Fabry disease.

- Later symptoms
 - **Progressive renal failure**, cardiovascular disease, heat/cold intolerance, **hypohidrosis** (decreased sweat production), hearing loss

DIAGNOSIS

LAB RESULTS

- Enzymatic assay for alpha galactosidase
- Genetic testing

TREATMENT

OTHER INTERVENTIONS

- Symptom management (e.g., analgesics)
- Enzyme replacement therapy
- Gene therapy

GAUCHER'S DISEASE

osms.it/gauchers-disease

PATHOLOGY & CAUSES

- **Most common** lysosomal storage disease
- Lysosomal enzyme **glucocerebrosidase** deficiency
- → Accumulation of sphingolipid glucocerebroside in cellular lysosomes, particularly macrophages resembling crumpled tissue paper (AKA Gaucher cells)
- Glucocerebroside also deposits in liver, spleen, bone marrow, bones, kidneys, lungs, central nervous system (CNS)
- **Autosomal recessive** pattern of inheritance

TYPES

- Three types based upon CNS involvement
 - Type I: absence of CNS involvement
 - Type II: acute neuronopathic form
 - Type III: subacute or chronic neuronopathic form

COMPLICATIONS

- Thrombocytopenia, anemia, bone disease, neurological deficits

SIGNS & SYMPTOMS

- **Hepatosplenomegaly**
- **Pancytopenia**, due to bone marrow infiltration with **Gaucher cells**, hypersplenism, leads to
 - Easy bruising (thrombocytopenia)
 - Fatigue (anemia)
- Bone disease (e.g., **osteoporosis**, **aseptic necrosis** of various **bones**); most commonly affects the **femur**
- Neurological complications (e.g. seizures, hypotonia, cognitive/olfactory abnormalities) present only in types II, III

DIAGNOSIS

LAB RESULTS

- Enzymatic assay to confirm glucocerebrosidase deficiency
- Genetic testing
 - Prenatal diagnosis available

TREATMENT

OTHER INTERVENTIONS

- Enzyme replacement therapy

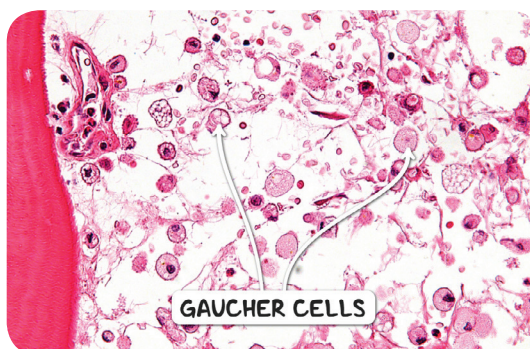


Figure 52.2 A section of bone marrow demonstrating numerous crinkled paper macrophages, or Gaucher cells, in an individual with Gaucher's disease.

KRABBE DISEASE

osms.it/krabbe-disease

PATHOLOGY & CAUSES

- AKA globoid cell leukodystrophy
- Lysosomal enzyme **galactocerebrosidase deficiency**
- Lipids galactocerebroside and psychosine buildup →
 - **Globoid cell** formation (multinucleated macrophages)
 - **Oligodendrocyte destruction** → demyelination
- **Autosomal recessive** inheritance pattern
- Progressive damage to nervous system → fatal

SIGNS & SYMPTOMS

- Usually present within first six months of life
- **Peripheral** motor, sensory **neuropathy**, loss of sensation, muscle atrophy in extremities

- Central nervous system dysfunction
 - Irritability, **developmental delay**, spasticity, **optic atrophy**, seizures, weakness

DIAGNOSIS

LAB RESULTS

- Enzymatic assay to measure galactocerebrosidase activity in leukocytes
- Microscopy shows demyelination, characteristic globoid cells (i.e., multinucleated macrophages containing ↑periodic acid-Schiff (PAS) positive materials)
- Genetic testing

TREATMENT

OTHER INTERVENTIONS

- Affective therapy not yet available
- Hematopoietic stem cell transplantation is beneficial, especially in early onset of symptoms

METACHROMATIC LEUKODYSTROPHY

osms.it/metachromatic-leukodystrophy

PATHOLOGY & CAUSES

- Lysosomal enzyme **arylsulfatase A** (ARSA) **deficiency** → ↑ cerebroside sulfate storage in various tissues, progressive **demyelination**
- Metachromatic leukodystrophy (MLD) also caused by saposine deficiency (i.e. protein that normally stimulates ARSA)
- **Autosomal recessive** inheritance pattern

COMPLICATIONS

- **Central, peripheral nervous** system dysfunction, paralysis, coma
- If untreated, fatal in 5–6 years

SIGNS & SYMPTOMS

- Usually develops in late infancy, but can also present later in life
- Infantile onset
 - Gait difficulties
 - Developmental delay

- Muscle tone, strength abnormalities
- **Ataxia**
- Peripheral neuropathy
- Progressive vision loss
- Late onset
 - Behavioral difficulties
 - Psychiatric disorder
 - **Dementia**

DIAGNOSIS

LAB RESULTS

- Enzymatic assay for ARSA
- Sulfatides measurement in urine to confirm diagnosis
- Genetic testing

TREATMENT

OTHER INTERVENTIONS

- Hematopoietic stem cell transplantation
- Gene therapy
- Enzyme replacement

NIEMANN–PICK DISEASE

osms.it/niemann-pick_disease

PATHOLOGY & CAUSES

- Group of disorders caused by defects in sphingomyelin storage
- Types A, B are characterized by enzyme acid **sphingomyelinase deficiency** → sphingomyelin accumulation in macrophage lysosomes in various tissues

- Type C is characterized by impaired cellular processing, low-density lipoprotein (LDL)-cholesterol transport
- **Autosomal recessive** inheritance pattern

COMPLICATIONS

- **Progressive neurodegeneration**, developmental delay, interstitial lung disease

SIGNS & SYMPTOMS

- **Hepatosplenomegaly**, hypersplenism → thrombocytopenia
- Various neurologic deficits
 - Ataxia, dysarthria, dysphagia, dystonia
- Developmental delay
- Interstitial lung disease, recurrent respiratory infections
- Lipid abnormalities
- Dementia/depression/bipolar disease/schizophrenia (in adults)
- **Macular cherry red spot** seen on fundoscopy examination
 - Fovea appears bright red compared to rest of retina where lipids are accumulated

DIAGNOSIS

LAB RESULTS

- Types A, B
 - Enzymatic assay for sphingomyelinase
- Type C
 - Impaired response to LDL-cholesterol in cultured fibroblasts
- Histology shows large **lipid laden macrophages** in reticuloendothelial system (AKA **foam cells**)
- Genetic testing

TREATMENT

- No treatment proven to modify onset/progression of disease

MEDICATIONS

- Miglustat (glycosphingolipids biosynthesis inhibitor) may be beneficial for type C

OTHER INTERVENTIONS

- Physical/occupational therapy, nutritional assessments



Figure 52.3 Numerous lipid-laden macrophages in the spleen of an individual with Niemann–Pick disease.

TAY-SACHS DISEASE

osms.it/tay-sachs_disease

PATHOLOGY & CAUSES

- **Hexosaminidase A deficiency** → glycolipid GM2 ganglioside buildup in neuronal lysosomes
- **Autosomal recessive** inheritance pattern

COMPLICATIONS

- Progressive neurodegeneration
- Mental/physical ability deterioration
- Death at ages 2–5, primarily → pneumonia

SIGNS & SYMPTOMS

- Typically presents at 2–6 months of age
- Progressive motor skill loss with hyperreflexia, hypotonia
- Physical ability deterioration
 - Blindness, deafness, dysphagia, dysarthria
- Milder symptoms in late onset Tay-Sachs disease
- **Cherry red spot macula** sign a characteristic finding on fundoscopy

DIAGNOSIS

LAB RESULTS

- Enzymatic assay for hexosaminidase A
- Genetic testing

TREATMENT

OTHER INTERVENTIONS

- Symptom reduction/infection prevention

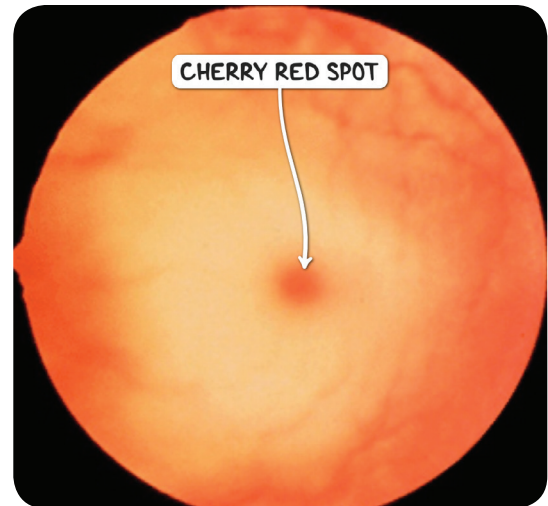


Figure 52.4 A cherry red spot on the retina of an individual with Tay-Sachs disease.